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| 10/700,032 | 11/03/2003 | Hani Sabbah | 1059.00096 | 3424 |

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| EXAMINER | |
|---|---|
| AFREMOVA, VERA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1657 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/700,032 | SABBAH ET AL. | |
| | Examiner | Art Unit | |
| | Vera Afremova | 1657 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-5 and 8-16* is/are pending in the application.

4a) Of the above claim(s) *3-5 and 8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 2, 15 and 16 as amended 8/06/2007 are pending and under examination.

Claims 3-5 and 8-14 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected groups of inventions. Applicant timely traversed the restriction requirement in the reply filed on 1/18/2006.

This application contains claims 3-5 and 8-14 drawn to invention(s) nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Claim Rejections - 35 USC § 112*

#### *New matter*

Claims 2, 15 and 16 as amended are/remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Insertion of the limitation "the products consisting essentially of the secretions from the mesenchymal stem cells" in the active step of administering stem cell products in the method of improving cardiac function has no support in the as-filed specification.

Insertion of the active step of "separating the mesenchymal stem cells from a supernatant, the supernatant containing products consisting essentially of secretions from the mesenchymal stem cells" and "improving cardiac function" as result of administering the "products consisting

essentially of the secretions from the mesenchymal stem cells" in the method of improving cardiac function has no support in the as-filed specification.

The insertion of these limitations and active steps is a new concept because they neither have literal support in the as-filed specification by way of a generic disclosure, nor there are specific examples of the newly inserted limitations and active steps that would show possession of the concept of the use of the products "consisting essentially of the secretions from the mesenchymal stem cells" for administering as a sole therapeutic agent without transplantation of stem cells or without mesenchymal stem cells in the method of improving cardiac function.

The generic disclosure of the as-filed specification indicates that "the purpose of the present invention is to utilize stem cells, supernatant from stem cells, the secretions resulting from the interaction of stem cells and other cells (e.g., stem cell products), or compounds that increase the amount of secretions present at a site, for treating heart failure" (specification page 4, lines 23-26). The as-filed specification teaches that the stem cells produce products at the site of administration, thereby, enhancing cellular function (specification page 9, lines 15-21).

Thus, the generic disclosure relates to the potential benefits of the stem cells in combinations with their secretions but not to the secretions alone as a sole therapeutic agent. The as-filed specification does not contain description of an *in vivo* administration of a sole product "consisting essentially of the secretions from the mesenchymal stem cells" to the patient in the method of improving cardiac function. The literal support is also missing for the phrase and/or term "products consisting essentially of the secretions from the mesenchymal stem cells".

Moreover, the generic disclosure in the as-filed specification defines the term "stem cells" as cells having ability to give rise to the hematopoietic lineage cells (page 6, lines 5-10).

Thus, the generic term "stem cells" is used in specification for the hematopoietic stem cells rather than for mesenchymal stem cells. Consequentially, the generic stem cell products would be understood as hematopoietic stem cell products. Although the bone marrow is a complex environment and it comprises both hematopoietic stem cells and mesenchymal stem cells, the generic term "stem cells" and /or abbreviated generic term "BMSC" (bone marrow stem cells) appear to relate in the as-filed specification to the hematopoietic stem cells rather than to the mesenchymal stem cells in view of the applicants' generic definitions in the as-filed specification. Therefore, the concept of the stem cell "products consisting essentially of secretions from the mesenchymal stem cells" was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention drawn to the use of "products consisting essentially of secretions from the mesenchymal stem cells".

The exemplified disclosure describes transplantation of cells (BMSC) but not of their secretions (page 22). The exemplified disclosure relates to an *in vitro* culturing of bone marrow cells or BMSC and observing expression of factors (page 23). The exemplified disclosure does not describe *in vivo* administration of products separated from the stem cells including the products separated from the mesenchymal stem cells. The exemplified disclosure of the active step of administering the products consisting essentially of the secretions from the stem cells in the method of improving cardiac function is lacking in the as-field specification. The exemplified disclosure of the active step of "administering the products consisting essentially of the secretions from the mesenchymal stem cells" in the method of improving cardiac function is lacking in the as-field specification.

Therefore, there is no sufficient support for the newly inserted limitations and active steps as drawn to an *in vivo* administration of stem cell secretions or of secretions of the mesenchymal stem cells as a sole therapeutic agent to the patient for improving cardiac function.

With regard to the active step of "separating the mesenchymal stem cells from a supernatant" it is noted that regardless the fact whether or not one of skill in the art would have known how to obtain and to separate a supernatant from the stem the instant rejection is a matter of a written description, not a question of what one of skill in the art would or would not have known. Moreover, the particular example describes that some of the factors that are produced by whole or mixed stem cell populations (BMSC) in an *in vitro* system and that are also regarded by applicants as beneficial for cardiac function (specification page 7) are not found in the culture medium with the BMSC (specification page 23, lines 26-29). Thus, the structural characteristic of those products that are "consisting essentially of secretions from the mesenchymal stem cells" of from mixed stem cells that would be separated from the stem cells and used as a sole therapeutic agent for *in vivo* administration without transplantation of the stem cells is not contemplated in the as-filed specification. Nor there is a description of a method of administering products "consisting essentially of secretions from the mesenchymal stem cells" or as a sole therapeutic agent to the patient for improving cardiac function.

The material within the four corners of the as-filed specification must lead to the claimed concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact.

Thus, the insertion of limitations and active steps of "separating the mesenchymal stem cells from a supernatant, the supernatant containing products consisting essentially of secretions

from the mesenchymal stem cells; and administering the products consisting essentially of the secretions from the mesenchymal stem cells" in the method of improving cardiac function is considered to be the insertion of new matter for the above reasons.

Applicant is hereby notified that the insertion of new matter into the claims has necessitated the removal of the art rejection over claims 2, 15 and 16 under 35 U.S.C. 102(b) as being anticipated by Pierpaolli et al. (Cellular Immunology. 1981. 57: 219-228). However, removal of new matter (broadening of claimed term from "mesenchymal stem cells" to "stem cell") will result in the reinstatement of the art rejection(s).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2, 15 and 16 as amended are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,368,636 (McIntosh et al.).

Claims are directed to a method of improving cardiac function by administering the products consisting essentially of the secretions from the MSCs, wherein the method comprises steps of isolating mesenchymal stem cells (MSC) from harvested marrow; growing the MSCs without differentiation in medium; enriching the medium containing the stem cells; separating the MSCs from a supernatant, the supernatant containing products consisting essentially of

secretions from the MSCs; administering the products consisting essentially of the secretions from the MSCs and improving cardiac function. Some claims are further drawn to the enriching step by exposing MSC to hypoxia. Some claims are further drawn to route of administration including intravenously, directly to the heart, etc.

US 6,368,636 teaches a method for reducing transplant rejection (entire document or col. 28, lines 3-7) including heart transplant (col. 5, line 38) by reducing immune response as result of administering the MSC supernatants (col. 6, lines 1-10) or "the products consisting essentially of the secretions from the MSCs", thereby, "improving cardiac function" within the broadest meaning of the instant claims. The MSC are isolated form bone marrow, expanded in culture and used for making the MSC supernatants (col. 9, lines 54-55 and col. 6, lines 5-6). The MSC are cultured under 5% carbon dioxide and 95% air (col. 14, line 43) and, thus, in the atmosphere with reduced oxygen amounts or under hypoxia within the broadest meaning of the instant claims.

Thus, the cited document anticipates the claimed invention.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 15 and 16 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over US 7,097,832 (Kornowski et al) and US 6,368,636 (McIntosh et al.).

Claims are directed to a method of improving cardiac function wherein the method comprises steps of culturing bone marrow derived mesenchymal stem cells and administering the products consisting essentially of the secretions from the stem cells. Some claims are further drawn to culturing the stem cells under hypoxia conditions for enrichment in the secretions from the stem cells. Some claims are further drawn to administering the products to the heart.

US 7,097,832 (Kornowski et al) teaches and/or suggest a method of improving cardiac function or treating ischemic myocardium wherein the method comprises steps of culturing bone marrow stem cells under hypoxia conditions for enrichment in the secretions from the stem cells (col. 16, lines 45-46; col. 9, lines 1-33) and administering bone marrow stem cells and the bone marrow secretion products (col. 17, lines 7-15; col. 15, lines 56-60). It is well known that bone marrow contains various stem cells including mesenchymal stem cells (MSC) and that MSC can be isolated, expanded in culture and used as source of MSC supernatant (US 6,368,636 at col. 9, lines 54-55 and col.6, lines 5-6). The cited US 7,097,832 clearly teaches that the bone marrow secreted factors are necessary to promote new blood vessel growth and to restore function of ischemic heart (col. 15, lines 44-46) and it also suggests administration of the bone marrow cell secretions to ischemic myocardium (col. 15, line 57 and col. 17, line 11-15).

The cited US 6,368,636 is relied upon for the teaching of additional beneficial effects of the MSC supernatants (col. 6, lines 1-10) such as reduction of transplant rejection including heart transplants (col. 5, line 38; col. 28, lines 1-10). Thus, the cited patent teaches and/or suggests reducing immune response by administering the MSC supernatants during heart transplantations and, thus, improving cardiac function within the broadest meaning of the instant claims. The MSC are cultured under 5% carbon dioxide and 95% air (col. 14, line 43) and, thus, in the

atmosphere with reduced oxygen amounts or under hypoxia within the broadest meaning of the instant claims.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to administer the bone marrow stem cell secretions to the ischemic hear with a reasonable expectation of success in improving cardiac function as taught and/or suggested by US 7,097,832. One of skill in the art would have been motivated to administer the bone marrow stem cell secretions for the benefits in promoting new blood vessel growth and restoring function of ischemic heart as taught and/or suggested by US 7,097,832. One of skill in the art would have been motivated to administer the MSC supernatants to reduced immune response during heart transplantation as suggested by US 6,368,636, thereby, improving cardiac function within the broadest meaning of the instant claims.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

***Response to Arguments***

Applicant's arguments filed 8/06/2007 and 5/29/2007 with respect to the presently amended claims (8/06/2007) have been fully considered but they are not found persuasive.

With regard to the claim rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement applicants present a long list of isolated phrases taken out of the specification context in attempt to demonstrate support for the claim

amendments. However, the citations intended for support mostly refer to the generic bone marrow stem cells (BMSC) that are not the mesenchymal stem cells as presently claimed in view of the applicants' specific definitions (page 6, lines 5-10). When the response citations explicitly indicate the mesenchymal stem cells, the corresponding text in the as-filed specification describes administration of the stem cells themselves but not of their secretions separated from the cells. Thus, arguments are not found persuasive.

Claim rejection under 35 U.S.C. 102(b) as being anticipated by Pierpaolli et al. (Cellular Immunology. 1981. 57: 219-228) has been withdrawn because the reference does not explicitly refer to the "mesenchymal stem cells" or their secretions. However, the removal of new matter (broadening of the claimed term) will result in the reinstatement of the art rejection.

With regard to the claim rejection under 35 U.S.C. 103(a) as being unpatentable over US 7,097,832 (Kornowski et al) applicants argue that the cited patent discloses a method for treating cardiac or myocardiac conditions by administering autologous marrow cells and it does not suggest the use of a supernatant separated from the bone marrow stem cells, and, therefore, there would not be any reasonable expectation in success. The argument is not found persuasive because the cited US 7,097,832 clearly teaches and recognizes the role of secretions of the bone marrow cells as factors necessary to restore the function of ischemic myocardium (entire document including col. 15, lines 44-46 col. 17, line 11-15) and, further, the separation of cells from the medium would have been obviously known to one having ordinary skill in the art at the time the claimed invention was made. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. The claimed subject matter

fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

The Declaration by Hani Sabbah filed on 12/15 2006 has been noted and revisited but it contains no data for consideration.

No claims are allowed.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

October 25, 2007

VERA AFREMOVA

PRIMARY EXAMINER